# REVIEW ARTICLE

## Adverse ocular reactions to drugs

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### Summary

**Drugs acting on various parts of the body may also affect the eye insidiously. Increased awareness of such drug toxicity by the prescribing doctor should encourage him to consider effects on the cornea, lens, retina, optic nerve and elsewhere when checking the patient's progress. The following review concerns adverse ocular effects of systemic drug administration.**

KEY WORDS: eye, drug toxicity.

### Eyelid, cornea and conjunctiva

Systemic drugs may give rise to conjunctival and corneal irritation, or the full-blown Stevens-Johnson syndrome. It is usual to find that the conjunctiva and cornea are affected at the same time.

Hypersensitivity reactions are common with aspirin taken at therapeutic dosage levels, producing angioneurotic oedema, erythema multiforme, haemorrhagic vasculitis as well as toxic epidermal necrolysis (Lyell's syndrome). Such severe reactions can lead to permanent ocular damage following the development of conjunctivitis, corneal ulceration, perforation and secondary glaucoma (Sainami and Balsara, 1970; Luria *et al.*, 1979). Transient myopia following aspirin intake has also been reported (Sandford-Smith, 1974).

The Stevens-Johnson syndrome may also be provoked by administration of chlorpropamide, sulphonamides, some anticonvulsants, and commonly prescribed nonsteroidal anti-inflammatory agents. The patient complains of ocular pain, irritation, discharge and photophobia.

Phenothiazines, particularly thioridazine, may give rise to dusky discoloration of the skin especially after many months at daily doses above 200 mg. This slate-blue skin discoloration involves not only exposed skin, but also the eyelids. It has been referred to as the 'purple people syndrome' (Mathalone, 1968)!

### Dry eye syndrome

Practolol, one of the earliest beta-blockers, caused a progressive dry eye syndrome, failure of tear production, corneal keratinization, conjunctival shrinkage in the fornices and symblepharon. The cornea became opacified, ulcerated and often perforated. These side effects occurred in only 0·2% of patients and the severity was directly proportional to the duration of drug administration. Studies have also shown the formation of an autoantibody which has an affinity for the intercellular zones of the squamous epithelium of the cornea (Garner and Rahi, 1976).

The 'practolol syndrome' has not been convincingly documented as occurring with other beta-blockers; and there is no reason to believe that any of these new drugs actually cause adverse ocular reactions (Wright, 1975; Furhoff, Norlander and Peterson, 1976), although isolated reports are found in the literature.

Like practolol, oxprenolol and propranolol have been associated with a reduced tear secretion, with or without cutaneous reaction (Editorial, 1976). Dry eyes have been reported after systemic use of timolol (Frais and Bayley, 1979). Although the adverse ocular effect is not as well developed as that seen with practolol, the similarity and the onset and partial clearing in relation to timolol therapy suggest a casual role (Van Buskirk, 1979). Dryness of the eyes (Simpson, 1979) and in another report, reduction of tear flow in 6 out of 18 treated cases (Besterman and Spencer, 1979) have also been observed with labetalol. There have been various reports of keratoconjunctivitis sicca with the systemic use of oxprenolol (Clayden, 1975; Lyall, 1975; Knapp and Galloway,

1975), but the evidence of any serious oculotoxicity is as yet tenuous.

Sedative tranquillizers, such as meprobamate, chlordiazepoxide and diazepam, when taken regularly over a long period of time, reduce tear production by the lacrimal gland, resulting in ocular irritation; it is reversible when the drug is stopped (Carreras and Matas, 1973).

### Corneal deposits

Some drugs, such as hydroxychloroquine, chlorpromazine, gold, indomethacin, pethidine (in an addict), clofazinine (used in leprosy and psoriasis) and recently amiodarone, have been reported to heap up in deposits on the cornea. Such deposits rarely cause a permanent deleterious effect on vision. There is a marked similarity in the corneal changes caused by these drugs, and the changes in the cornea in patients with Fabry's glycolipidosis (Ingram, 1978).

Chloroquine keratopathy was first described by Hobbs and Calnan (1958). The incidence is high, corneal deposits appearing in about 30–70% of treated patients and may be present after one to two months of treatment at full therapeutic dosage (Eukensen, 1979). No ocular toxicity follows a low dosage schedule of 250 mg on alternate days, limited to courses of 9 months with drug-free breaks of 6 months during which the drug is slowly excreted and the corneal deposits disappear (Mikkelsen, 1979). The keratopathy appears on slit-lamp examination as a series of punctate opacities scattered diffusely over the cornea, whilst thicker yellow-green lines may be found in the stroma. Chloroquine keratopathy occurs with all types of chloroquine, and is not related to the toxic retinopathy that may develop with the drug. It is often asymptomatic, with less than 50% of patients with corneal change having any visual complaint.

Chloroquine keratopathy should never be considered a reason for termination of therapy, except in patients in whom it is causing symptoms of haloes around lights, photophobia and blurred vision. It is usually completely reversible on stopping treatment.

Chlorpromazine has also been found to produce golden-brown granules in the conjunctiva with similar fine deposits in the corneal stroma and Descemet's membrane; this is also reversible after the drug has been discontinued (Rasmussen, Kirk and Faurbye, 1980).

Gold, used in the treatment of rheumatoid arthritis, causes deposits of dust-like granules in the cornea, especially in the sub-epithelial layer, and the conjunctiva. This phenomenon is known as chryseosis corneae and is dose-related (Rodenhauser and Behrend, 1969). The deposits do not affect corneal transparency and therefore visual activity remains unaltered. The deposits may be associated with keratoconjunctivitis. Some feel that gold keratopathy is now less of a problem than formerly, because of newer preparations given in smaller doses at less frequent weekly intervals.

Amiodarone is an effective anti-anginal drug and versatile anti-arrhythmic agent. The development of corneal micro-deposits was first reported in 1968 by Joseph and Rouselie. Many reports have since followed describing the incidence and epidemiology of this curious phenomenon: therapeutic doses of amiodarone to 8 patients resulted in the formation of vortex-like figures within the anterior chamber of the eye (D'Amico, Kenyon and Ruskin, 1981). The deposits, which histologically consist of lipofuchsin, can only be seen with the slit-lamp microscope. They are found essentially in the interpalpebral space below the pupil, at the junction of the middle third and lower third of the corneal surface. They are yellowish-brown in colour, becoming browner when the deposits are large and concentrated (Babel and Stangos, 1972). Radioisotope studies have shown that amiodarone passes into the tears, and is in this way deposited on the surface of the palpebral slit (Verin et al., 1972). This is also seen with chloroquine, but this drug can also be fixed in the ocular fundus, resulting in lesions by progressive accumulation in the pigmented structures. The chorio-retina is never involved with amiodarone. It is therefore possible to avoid routine observation of the various parameters of the ocular fundus (perimetry, angiography, electroretinography) (Verin and Vildy, 1978). Treatment should therefore not be interrupted in the presence of corneal deposition in the absence of symptoms; but if symptoms are present, such as reduced visual acuity and coloured haloes, temporary suspension of the drug will allow the deposits to regress. The ocular risk is extremely slight in the context of treating a wide variety of patients suffering from cardiac arrhythmias, many of which are of types notoriously unresponsive to conventional drugs (Ingram, 1978). Ophthalmic supervision is desirable at the moment, though strict supervision may become impractical in the future as the drug becomes widely used.

### Lens

Toxic cataract is uncommon. Many cases appeared in the 1930's as a result of the injection of dinitrophenol, a drug taken to suppress the appetite. Other offenders include triparanol (MER/29) and, nowadays, oral steroids administered over a long period. Some of the phenothiazines, used primarily in psychiatric disorders, have also been reported to cause lens opacities.

Prolonged systemic corticosteroids may give rise to posterior polar lens opacities. Initially in the posterior

sub-capsular area of the lens, the opacity spreads to the lens equator and the sub-capsular level, and finally, in a few patients, anterior sub-capsular opacities with nuclear changes are seen. Such changes develop slowly and are dose-related. Those on higher doses of steroids develop their cataracts quicker, more frequently and to a more severe degree than patients on low doses. The crucial dose appears to be the equivalent of prednisolone 10 mg daily for one year; and the incidence of posterior sub-capsular cataract in such patients seems to be about 10% (Greiner and Chylack, 1979; Lubkin, 1977). A change in permeability of the capsule followed by a change in electrolyte concentration in the lens, as well as a change of the mucopolysaccharide of the lens have been advanced as causes for the development of the cataract (Kaiser, 1977). The degree of reduction of visual acuity is variable.

Following prolonged use, phenothiazines can cause lens deposits, mainly of an anterior polar variety. The lens changes have mainly been observed in patients on chlorpromazine, where fine yellowish-brown granules can be seen beneath the anterior lens capsule. They are rarely seen in patients on trifluoperazine and thioridazine. The deposits are rarely sufficient to interfere with vision (Siddall, 1965).

Rarely, some patients experience an acute transient myopia when taking tetracyclines, sulphonamides, antihistamines or acetazolamide. The symptoms of blurred vision on distant accommodation come on hours to days after ingestion. It is thought that this is due to transient hydration of the lens, leading to its greater thickening, and resulting in a myopic eye. The condition is reversible on stopping the drug (Davidson, 1980).

## Retina

Drugs may cause retinopathy, optic neuritis or papilloedema. Since they present a serious threat to vision in susceptible individuals, early recognition is essential (Sloan Wilson, Fraunfelder and Landers, 1979).

### Retinopathy

This is of extreme importance because drug toxicity affects the outer layers of the retinal pigment epithelium, receptor cells and outer nuclear layer, leading to progressive visual loss. The most common and severe drug-induced retinopathies are due to the chloroquine family of drugs, and to chlorpromazine. Macular oedema may occur with allopurinol, indomethacin, oral contraceptives and quinine.

### Chloroquine retinopathy

Chloroquine and related drugs, originally antimalarial drugs, are now widely used in the treatment of discoid and systemic lupus erythematosus, rheumatoid arthritis and sarcoidosis. Chloroquine-induced retinopathy was first described in 1957 by Cambiaggi. Chloroquine binds to melanin and inhibits amino acid incorporation into the retinal pigment epithelium (Gonasun and Potts, 1974). Chloroquine maculopathy classically consists of alternate circular layers of a lighter area of depigmentation which is itself encompassed by a dark ring of pigmentation—the 'bull's eye' macula. In the early stages, there are changes in the macular retinal pigment epithelium; usually a mottled appearance at the macula is first seen followed by a pigmentary clumping causing a reduction in visual acuity (Henkind, Carr and Sigel, 1964). The picture is however not always clear.

The incidence of chloroquine retinopathy in different series has varied from less than 1% to more than 15% depending on the definition of what constitutes a retinopathy, and the method used for its detection. The two most important tests for ocular toxicity are charting of the central field to a red target and the ophthalmoscopic examination of the fovea. Both are simple and quick but should be performed serially (Marks and Power, 1979). Testing of retinal thresholds to red light in dark-adapted subjects and fundus fluorescein angiography have also been used (Carr, Gouras and Gunkel, 1966). Testing of colour vision, Amsler charting, perimetry, central field charting to white objects, and serial photography are of no value in screening patients for ocular toxicity. The electrooculogram and electroretinogram can be abnormal in the early stages, but changes are not always present and not pathognomonic. The foveal reflex tends to become lost and the macula pigment irregular with advancing age; but loss of the foveal reflex remains a useful guide if the patient has normal and youthful maculae before therapy is begun.

Patients should have an initial examination before therapy is begun, with repeat tests after a year and thence at 4-monthly intervals (Van Lith, 1980). Each examination should include the recording of central fields to a red target, and examination of the macula and foveal reflex under mydriasis. If the central field is at any time abnormal, therapy should be discontinued. The patient should be taught to carry out a simple visual acuity check on himself. Dosage plays an important role, the critical toxic level being over 250 mg a day for chloroquine or 200 mg a day for hydroxychloroquine. The daily dosage is of greater importance than the duration of treatment or cumulative dose (Rynes, Krobel and Falbo, 1979; Rosenbaum, 1979). The most common cause of visual symptoms is a transient rise in presbyopia, which may occur soon after therapy is begun, especially if high doses are used. Other functional defects include

difficulty in reading, scotoma, defective colour vision, photophobia and flashes of light. Symptoms do not run parallel with retinal changes. The prognosis of retinopathy is uncertain.

Improvement may follow the discontinuation of chloroquine therapy in the early stages; in many cases however, deterioration continues progressively (Brinkley, Dubois and Ryan, 1980; Ogawa et al., 1979). The presence of nephropathy or the concommittant use of the probenecid increases the likelihood of the development of the retinopathy (Frankel, 1975). Patients with systemic lupus erythematosus are more susceptible than patients with rheumatoid arthritis (Elman et al., 1976).

Phenothiazines cause a retinopathy that is both dose- and duration-related, resulting in a diffuse pigmentary retinopathy with altered vision. It has been reported that phenothiazines with the piperidine rings have a higher risk of producing retinal toxicity. Thioridazine is the major phenothiazine in this group (Meredith, Aaberg and Willesson, 1978; McAuliffe and Mooney, 1978). The critical toxic level is 800 mg/day. Only a few cases of chlorpromazine retinopathy have been reported (Siddall, 1965). Interestingly, the retinopathy may present either acutely with sudden loss of vision associated with retinal oedema and hyperaemia of the optic disc, or chronically with a fine pigment scatter appearing in the central area of the fundus extending peripherally but sparing the macula. Paracentral and pericentral scotomas may be found in their chronic types.

The possible retinal vascular toxic effects of oral contraceptives are controversial, but include occlusion, haemorrhage and oedema. The additive effects of cigarette smoking together with these drugs is also under observation (Gombos, Moreno and Bedrossian, 1975).

Busulphan therapy given for chronic myeloid leukaemia in a pregnant mother has been reported as causing pigmentary degeneration of the retina in the offspring (Crombie, 1981).

## Optic neuritis

Inflammation of the optic nerve has been reported with several drugs. Classic symptoms and findings include decreased central vision (usually bilateral), field defects, mainly central loss, and swelling of the optic nerve head which may be subtle. These changes may be due to neurotoxicity or vascular involvement, the former being more common. The drugs include: chloramphenicol, streptomycin, isoniazid, ethambutol, penicillamine, quinine, digitalis, oral contraceptives, arsenicals, alcohol, ibuprofen and chlorpropamide. If the drug is stopped, most of the clinical features usually abate.

Chloramphenicol has been found to produce optic hyperaemia, a few haemorrhages, and central and paracentral scotomas. Later on, optic atrophy supervenes. There is some evidence of faulty vitamin $B_{12}$ metabolism in these cases and, on occasion, the antibiotic has been used again in the same patient in conjunction with vitamin $B_{12}$ without any deleterious effect on vision (Begg, Small and White, 1967). Chloramphenicol has been noted to lead to optic neuritis, especially in children with fibrocystic disease of the pancreas (Corke, 1967). Toxicity occurs with high dosage of more than 6 weeks. Its withdrawal restores normal vision.

Ethambutol is effective against mycobacteria by blocking nucleic acid synthesis. It is currently used in combination with other tuberculostatics of the first order. The dosage should be modified depending on renal function. The ocular system is the main target of ethambutol toxicity. The incidence of ocular damage, mostly optic neuritis and colour vision defects, varies according to different authors from 3 to 6% of treated patients (Lahlou et al., 1980). Patients complain of increased difficulty in reading, tired eyes, spots in the visual field, reduction of green vision and restricted visual field. The toxic effect is dose-dependent, and in regimens employing a dose of 10 to 15 mg/kg/day no ocular toxicity has been observed. Serious changes with irreversible optic atrophy, as well as retinal defects with pigment displacement and haemorrhages, occur with doses as high as 25 mg/kg/day or more. The time of onset of impairment in vision varies from 3 to 6 months after starting the drug (Prachakvej and Subharngkasen, 1978). Pre-existing liver damage or diabetic changes in the fundus of the eye appear to predispose to visual disturbances (Meyer and Hoigne, 1980). In such patients, colour vision as well as visual acuity should be tested before the onset of therapy, and thereafter every 2 or more weeks during the treatment, using colour tables and reading tests. All patients should be warned of the oculotoxicity of the drug, and should they complain of visual disturbance, discontinuation of ethambutol treatment must be considered immediately especially if the ophthalmic examination confirms the adverse reaction (Meyer and Hoigne, 1980).

Cessation of ethambutol medication and administration of vitamin $B_{12}$ resulted in a cure in 61% of patients analysed by Harada, Sakate and Schikawa (1979). The rest did not regain their visual acuity. In some patients, ocular damage may be preceded by the development of peripheral neuropathy. In such cases, the symptoms of peripheral neuropathy may serve as a warning for the subsequent development of more serious visual toxicity (Nari, LeBrun and Kass, 1980).

Isoniazid causes optic neurotoxicity, in particular impairment of red-green perception, in doses of 200–900 mg/day. The co-administration of pyridox-

ine in a dose of 25–100 mg/day reduced the incidence (Feldmann and Barlehen, 1977). Streptomycin causes xanthopsia with central scotoma leading to blindness with optic atrophy (Davidson, 1980). Sulphonamides, used extensively in the past, were reported to produce optic neuropathy. Oral hypoglycaemic agents such as tolbutamide and chlorpropamide have been reported to produce toxic amblyopia (George, 1963). Digitalis-induced ocular symptoms are rare. They include blurred vision and a reduction in visual acuity and colour vision. Objects may appear yellow (xanthopsia) or less often green, brown, red, 'snowy' or white. Other symptoms include photophobia and flashes of light. Scotomas and rarely transient and permanent amblyopia have been described. The effects are due to either a direct action on the retinal receptor cells, or to retrobulbar neuritis or may be of central origin i.e. involvement of the occipital cortex (Meyer and Hoigne, 1980).

## Papilloedema

Swelling of the optic nerve papillae, usually without visual loss, is occasionally seen with corticosteroid therapy or its withdrawal, oral contraceptives, tetracycline, nalidixic acid and hypervitaminosis. During the past years the term 'benign intracranial hypertension' has been used to describe a relatively rare disease entity consisting primarily of a benign elevation of intracranial pressure. The cerebrospinal fluid findings are completely normal, and computed brain-tomography shows small ventricular space with no evidence of a space-occupying lesion. Clinically, there is swelling of the optic nerve head and enlargement of the blind spot. This condition can be caused by tetracyclines (Ohlrich and Ohlrich, 1977), nalixidic acid (Boreus and Sundstrom, 1967), systemic steroids (Cluff, Caranasos and Stewart, 1975) and hypervitaminosis A (Lombaert and Carton, 1976) and D (Jung and Courvoisier, 1980).

The disc oedema usually resolves on stopping the drug. Hypervitaminosis D can also cause a sluggish pupillary reaction, iritis and cataract. More commonly it causes a band keratopathy due to calcium deposits on the cornea.

## Intraocular pressure

In predisposed eyes (patients over 30 years of age with narrow angles and shallow anterior chambers), systemically administered drugs with an anticholinergic action that produces pupillary dilatation have at times induced angle closure glaucoma. Such drugs include atropine, gastrointestinal spasmolytic agents, antihistamines, antiparkinsonian agents and psychotropic drugs.

Atropine and related synthetic drugs when given pre-operatively or for gastrointestinal disorders, may cause blurred vision in presbyopic patients. This is due to a direct action on accommodation, such agents tending to dilate the pupils, so that in patients with narrow anterior chamber angles there is an added threat of angle closure glaucoma. There has been widespread concern regarding the possible adverse ocular effects of both the monoamine oxidase inhibitors and the tricyclic antidepressants. These effects mainly occur in predisposed patients (described above) or in those already suffering from open angle glaucoma. The added anticholinergic effects of mydriasis and mild cycloplegia could trigger a fullblown acute attack of narrow angle glaucoma. However, it is to be noted that the evidence for such reports is indeed sparse and such drugs are not contra-indicated in primary glaucomatous condition, as the standard anti-glaucoma therapy will easily counterbalance any possibility of aggravation of the condition by the drugs.

## Oculomotor involvement

Phenobarbital and phenytoin may have oculomotor effects including nystagmus, weakness of convergence and of accommodation. The degree of oculomotor abnormality is related to drug dosage and may be present for several months after stopping the drug. The earliest abnormality that may be detected on examination of extraocular movements is that of broken pursuit.

The piperazine group of phenothiazines, including trifluoperazine, perphenazine and prochlorperazine may cause extrapyramidal syndromes with extraocular muscle involvement. Oculogyric crisis is a well known consequence of phenothiazine toxicity.

## Conclusion

In 1974, Grant in his encyclopaedic work on the toxicology of the eye quite rightly remarked that many new reports flow in daily concerning drugs involving the ocular apparatus. The risks inherent with drug administration and drug toxicity are always present and should never be taken lightly. The above review has dealt with the more important recognized ocular adverse reaction to drugs in current systemic use. We hope it will serve as a clinical guideline to practicing physicians.

## Acknowledgments

## References

BABEL, J. & STANGOS, N. (1972) Action of amiodarone on ocular tissues. *Schweizerische medizinische Wochenschrift*, **102**, 220.
BEGG, I.S., SMALL, M. & WHITE, A.M. (1968) Chloramphenicol. *Lancet*, **ii**, 686.
BESTERMAN, E.M.M. & SPENCER, M. (1979) Open evaluation of

labetalol in treatment of angina pectoris in hypertensive patients. *British Journal of Clinical Pharmacology, 8,* 2055.

BOREUS, L.O. & SUNDSTROM, B. (1967) Intracranial hypertension in a child during treatment with nalidixic acid. *British Medical Journal, 2,* 744.

BRINKLEY, J.R., DUBOIS, E.L. & RYAN, S.J. (1979) Long-term course of chloroquine retinopathy after cessation of medication. *American Journal of Opthalmology, 88,* 1.

CAMBIAGGI, A. (1957) Chloroquine-induced retinopathy. *Archives of Ophthalmology, 57,* 451.

CARR, R.E., GOURAS, P. & GUNKEL, R.D. (1966) Chloroquine retinopathy. *Archives of Ophthalmology, 75,* 171.

CARRERAS, Y. & MATAS, M. (1973) Mogadon, aspirina y secrecion lagrimol. *Revista española de oto-neuro-oftalmologia y neurocirugia, 31,* 245.

CLAYDEN, J.R. (1975) Ocular reactions to beta-blockers. *British Medical Journal, 2,* 557.

CLUFF, L.E., CARANOSIS, G.J. & STEWART, R.B. (1975) Ocular manifestations. *Major Problems in Internal Medicine, 5,* 207.

CORKE, J.G. (1967) Chloramphenicol optic neuritis. Apparent protective effects of very high daily dose of pyridoxine and cyanocobalamin. *American Journal of Diseases of Children, 114,* 424.

CROMBIE, A.L. (1981) Drugs causing eye problems. *Prescribers' Journal, 21,* 499.

D'AMICO, D.J., KENYON, K.R. & RUSKIN, J.N. (1981) Amiodarone keratopathy: Drug-induced lipid storage disease. *Archives of Ophthalmology N.Y., 99,* 257.

DAVIDSON, S.I. (1980) Drug-induced disorders of the eye. *British Journal of Hospital Medicine, 2,* 2.

EDITORIAL (1976) Beta-blockers and the eye. *British Journal of Ophthalmology, 60,* 311.

ELMAN, A., CULLBERG, R., NILSON, E., RENDAHL, I. & WACHTMEISTER, L. (1976) Chloroquine retinopathy in patients with rheumatoid arthritis. *Scandinavian Journal of Rheumatology, 5,* 161.

EUKENSEN, L.F. (1979) Chloroquine keratopathy in chloroquine workers after topical dust exposure. *Acta ophthalmologica, 57,* 823.

FELDMANN, H.U. & BARLEHEN, P. (1977) Medikamentenbedingte Hautausschlage. *Medizin (Erlangen), 5,* 75.

FRAIS, M.A. & BAYLEY, T.J. (1979) Ocular reactions to timolol meleate. *Postgraduate Medical Journal, 55,* 884.

FRANKEL, E.B. (1975) Visual defect from chloroquine phosphate. *Archives of Dermatology, 111,* 1069.

FURHOFF, A.K., NORLANDER, M. & PETERSON, C. (1976) Ocular reactions to beta-blockers. *British Medical Journal, 1,* 831.

GARNER, A. & RAHI, A.H.S. (1976) Practolol and ocular toxicity. *British Journal of Ophthalmology, 60,* 311.

GEORGE, C.W. (1963) Central scotomata due to chlorpropamide. Case report. *Archives of Ophthalmology, 69,* 773.

GOMBOS, G.M., MERENO, D.H. & BEDROSSIAN, P.B. (1975) Retinal vascular occlusion induced by oral contraceptives. *Annals of Ophthalmology, 7,* 215.

GONASUN, L.M. & POTTS, A.M. (1974) *In vitro* inhibition of protein synthesis in the retinal pigment epithelium by chloroquine. *Investigative Ophthalmology, 13,* 107.

GRANT, W.M. (1974) *Toxicology of the eye.* 2nd edn. Charles C. Thomas, Springfield, Illinois.

GREINER, J.V. & CHYLACK, L.T., Jr (1979) Posterior subcapsular cataracts: histopathological study of steroid-associated cataracts. *Archives of Ophthalmology, 97,* 135.

HARADA, T., SAKATE, S. & SCHIKAWA, H. (1979) Ocular toxicity with ethambutol. *Rinsho Ganka, 33,* 1345.

HENKIND, P., CARR, K. & SIGEL, J. (1964) Early chloroquine retinopathy. *Archives of Ophthalmology, 1,* 157.

HOBBS, H.E. & CALNAN, C.D. (1958) Chloroquine keratopathy. *Lancet, i,* 1207.

INGRAM, D.U. (1978) Ocular changes during oral amiodarone treatment. *R.S.M. International Congress & Symposium,* series No. **16,** p. 57.

JOSEPH & ROUSELIE (1968) Ocular changes with amiodarone. *Round table Seminar on admiodarone.* Paris.

JUNG, A. & COURVOISIER, B. (1980) Intoxication par la vitamine D. *Schweizerische medizinische Wochenschrift, 110,* 1972.

KAISER, H. (1977) *Cortison derviate in klinik und praxis,* 7th Edn. G. Thieme, Stuttgart.

KNAPP, M.A. & GALLOWAY, N.R. (1975) Adverse effects on oxprenolol. *British Medical Journal, 2,* 557.

LAHLOU, G., RASPILLER, A., GRANGE, G., ZUCK, P. & LAMAZE, R. (1980) La neuropathie optique a l'ethambutol a propos de 7 observations. *Annales Médicales de Nancy et de l'Est. 106,* 733.

LOMBAERT, A. & CARTON, H. (1976) Benign intracranial hypertension due to A-hypervitaminosis in adults and adolescents. *European Neurology, 14,* 340.

LUBKIN, V.L. (1977) Steroid cataract—a review and conclusion. *Journal of Asthma Research, 14,* 55.

LURIA, S.M., KINNEY, J.A.S., McKAY, L.L., PAULSON, J.M. & RYAN, A.P. (1979) Effects of aspirin and dimenhydrinate on visual processes. *British Journal of Clinical Pharmacy, 7,* 585.

LYALL, J.R.W. (1975) Adverse effects of beta-blockers, *British Medical Journal, 2,* 747.

McAULIFFE, D.C. & MOONEY, D. (1978) Thioridazine retinopathy. *Irish Journal of Medical Science, 147,* 225.

MARKS, J.S. & POWER, B.J. (1979) Is chloroquine obsolete in the treatment of rheumatic disease? *Lancet, i,* 371.

MATHALONE, M.B.R. (1968) Ocular effects of phenothiazine derivatives and reversibility. *Diseases of the Nervous System.* **29,** (Suppl. 3), 29.

MEREDITH, T.A., AABERG, T.M. & WILLESSON, W.D. (1978) Progressive chorioretinopathy after receiving thioridazine. *Archives of Ophthalmology, 96,* 1172.

MEYER, H. & HOIGNE, R. (1980) Drugs used in tuberculosis. *Meyler's side effects of drugs.* 9th edition. Excerpta Medica.

MIKKELSEN, J. (1979) Ojenkomplikationer ved behandling med antimalariamidler dermatologien. *Ugeskrift for Læger 141,* 2316.

NARI, S., LEBRUN, M. & KASS, I. (1980) Peripheral neuropathy associated with ethambutol. *Chest, 77,* 98.

OGAWA, S., KURUMATANI, N., SHIBARKE, N. & YAMAZOE, S. (1979) Progression of retinopathy long after cessation of chloroquine therapy. *Lancet, i,* 1408.

OHLRICH, G.D. & OHLRICH, J.G. (1977) Papilloedema in an adolescent due to tetracyclines. *Medical Journal of Australia, 1,* 334.

PRACHAKVEJ, P. & SUBHARNGKASEN (1978) Visual loss from ethambutol clinical observations of 7 patients. *Journal of the Medical Association of Thailand, 61,* 497.

RASMUSSEN, K., KIRK, L. & FAURBYE, A. (1980) Deposits in the lens and cornea of the eye during long-term chlorpromazine medication. *Acta Psychiatrica Scandinavica, 53,* 1.

RODENHAUSER, J.H. & BEHREND, T. (1969) Art und Haufiegkeit der Augenbeteiligung nach parenteraler goldtherapie. *Deutsche medizinische Wochenschrift, 46,* 2389.

ROSENBAUM, E.E. (1979) *Chloroquine in rheumatology—new directions of therapy,* p. 20. Med. Exam. Publishing, New York.

RYNES, R.I., KROBEL, G. & FALBO, A. (1979) Ophthalmological safety of long-term hydroxychloroquine treatment. *Arthritis and Rheumatism, 22,* 832.

SAINAMI, G.S. & BALSARA, A.B. (1970) Stevens-Johnson syndrome. *Journal of the Indian Medical Association, 54,* 512.

SANDFORD-SMITH, J.H. (1974) Transient myopia after aspirin. *British Journal of Ophthalmology, 58,* 698.

SIDDALL, J.R. (1965) The ocular toxic findings with prolonged and high dosage chlorpromazine intake. *Archives of Ophthalmology, 74,* 460.

SIMPSON, F.O. (1979) A multicentre open trial of Labetalol in New Zealand. *British Journal of Clinical Pharmacology, 8,* 1795.

SLOAN WILSON, R., FRAUNFELDER, P.T. & LANDERS, J.H. (1979) The National registry of drug-induced ocular side-effects and toxic drug effects on the retina. *Journal of the Arkansas Medical Society, 76,* No. 4.

VAN BUSKIRK, E.M. (1979) Corneal anaesthesia after timolol maleate therapy. *American Journal of Ophthalmology, 88,* 739.

VAN LITH, G.H.M. (1980) Is oogheelkundije controle big gebruik van chloroquine (derivaten) altijd noodzakelijk? *Nederlandsch tijdschrift voor geneeskunde,* **124,** 1866.

VERIN, P.H., BLANQUET, P., GENDRE, P.H. & SEKKAT, A. (1972) *Bulletin de la Société belge d'ophthalmologie,* **160,** 591.

VERIN, P.H. & VILDY, A. (1978) Oculo-cutaneous effects of amio-darone. *R.S.M. International Congress & Symposium Series,* No. 16, p. 62.

WRIGHT, P. (1975) Ocular reactions to beta-blockers. *British Medical Journal,* **1,** 831.